New onset geriatric epilepsy
A randomized study of gabapentin, lamotrigine, and carbamazepine

A.J. Rowan, MD; R.E. Ramsay, MD; J.F. Collins, ScD; F. Pryor, MPH; K.D. Boardman, RPh; B.M. Uthman, MD; M. Spitz, MD; T. Frederick, MD; A. Towne, MD; G.S. Carter, MD, PhD; W. Marks, MD; J. Felicetta, MD; M.L. Tomyanovich, MD; and the VA Cooperative Study 428 Group

Abstract—Objective: To determine the relative tolerability and efficacy of two newer antiepileptic drugs, lamotrigine (LTG) and gabapentin (GBP), as compared to carbamazepine (CBZ) in older patients with epilepsy. Methods: This was an 18-center, randomized, double-blind, double dummy, parallel study of 593 elderly subjects with newly diagnosed seizures. Patients were randomly assigned to one of three treatment groups: GBP 1,500 mg/day, LTG 150 mg/day, CBZ 600 mg/day. The primary outcome measure was retention in trial for 12 months. Results: Mean age was 72 years. The most common etiology was cerebral infarction. Patients had multiple medical conditions and took an average of seven comediations. Mean plasma levels at 6 weeks were as follows: GBP 8.67 ± 4.83 μg/mL, LTG 2.87 ± 1.60 μg/mL, CBZ 6.79 ± 2.92 μg/mL. They remained stable throughout the trial. Early terminations: LTG 44.2%, GBP 51%, CBZ 64.5% (p = 0.0002). Significant paired comparisons: LTG vs CBZ: p < 0.0001; GBP vs CBZ: p = 0.008. Terminations for adverse events: LTG 12.1%, GBP 21.6%, CBZ 31% (p = 0.001). Significant paired comparisons: LTG vs CBZ: p < 0.0001; LTG vs GBP: p = 0.015. There were no significant differences in seizure free rate at 12 months. Conclusions: The main limiting factor in patient retention was adverse drug reactions. Patients taking lamotrigine (LTG) or gabapentin (GBP) did better than those taking carbamazepine. Seizure control was similar among groups. LTG and GBP should be considered as initial therapy for older patients with newly diagnosed seizures.

Epidemiologic data indicate that the incidence of epilepsy increases markedly after age 60, exceeding that of any other age group, including children, by several fold. Factors complicating the treatment of seizures in older age groups include concurrent medical diseases, polytherapy, changes in pharmacokinetics (pK), and altered CNS pharmacodynamics. Many antiepileptic drugs (AEDs) pose problems in the aged due to limited tolerability. With the introduction of gabapentin (GBP) in 1993 and lamotrigine (LTG) shortly thereafter, both appeared to have favorable pK and side effect profiles that might offer treatment benefits. One controlled study found that carbamazepine (CBZ) was less well tolerated than LTG in the treatment of older patients with new onset seizures. These considerations led us to design a clinical trial of both GBP and LTG in elderly patients with newly diagnosed epileptic seizures, using CBZ, widely considered to be a drug of choice for partial onset seizures, as a comparator.

Methods. The study commenced in 1998 at 18 Veterans Affairs Medical Centers. The design, similar to that of two previous VA studies, was modified for the elderly population. Approval was obtained from the central VA Human Rights Committee and all local institutional review boards. All participants gave their informed consent. Initially, patients aged 65 and older with newly diagnosed seizures of any type were randomly assigned to blinded treatment with GBP, LTG, or CBZ. After the first year, age at entry was lowered to 60 to improve enrollment. Clinical evaluations were carried out at enrollment, biweekly to week 8, monthly to week 28, and bimonthly to week 52. Patients remaining in the study for a second year were evaluated every 3 months. Patients continued on the assigned AED until the end of the trial, or until they exited the study for any reason.

Additional material related to this article can be found on the Neurology Web site. Go to www.neurology.org and scroll down the Table of Contents for the June 14 issue to find the title link for this article.
Entry criteria. Eligible patients were newly diagnosed with epilepsy (97/1358; 7.1%), see table E-1). Unknown causes accounted for 24.0% (442/1879), which was cerebral infarction (177/592; 29.9%), followed by arteriosclerosis (93/592; 15.7%) and head trauma (42/592; 7.1%), see table E-1. The majority of patients had vascular disease as evidenced by concurrent medical problems such as hypertension (391/592; 65.9%), stroke (302/593; 50.9%), and cardiac disease (298/592; 50.3%), which were the most common of the principal investigator in concert with a patient-investigator telephoning the study's Data Coordinating Center (DCC) where a staff member assigned a nonconsecutive, site-specific patient number from a computer generated randomization list. This patient number corresponded to a patient drug kit in the site's pharmacy. A prescription for the specified drug kit was then prepared for the patient, who usually took the first dose of study drug at enrollment 239 patients (40.3%) were taking enzyme-inducing medications were allowed save chronic AEDs. Additional exclusions that would significantly affect the response to treatment. All comedication use excepting those conditions likely to lead to a life expectancy of less than 12 months, progressive neurologic disease, or conditions that would significantly affect the response to treatment. All comedications were allowed save chronic AEDs. Additional exclusion criteria included those with severe psychiatric conditions, current alcoholism, illicit drug use, or a history of noncompliance.

Study design. This was a randomized, double-blind, parallel trial comparing three monotherapy treatments: GBP (target dose: 1,500 mg/day), LTG (target dose: 150 mg/day), and CBZ (target dose: 600 mg/day). Subjects received two dosage forms labeled alpha and beta (capsules). Alpha was LTG 25 mg or matching placebo given twice daily; beta was GBP 300 mg, over-encapsulated CBZ 200 mg tablets, or placebo given three times daily. All patients were randomized to receive one active and one placebo formulation with equal numbers entered into each treatment arm. GBP was started at 300 mg/day and increased by 300 mg/day every 3 days to the target of 1,500 mg/day. LTG was titrated at 25 mg/day for 2 weeks, 50 mg/day for 2 weeks, 100 mg/day for 2 weeks, followed by 150 mg/day. CBZ was increased by 200 mg every 2 weeks to 600 mg/day. It is emphasized that target doses were estimated of effective, well-tolerated doses in this population. They were not intended to be fixed throughout the study. Incremental increases above target were allowed at any time if seizure control was inadequate. Similarly, incremental decreases were allowed if the patient experienced toxicity. AEDs being taken at enrollment were tapered to zero during titration of study drug. At enrollment 239 patients (40.3%) were taking enzyme-inducing AEDs, 219 (39.6%) of whom were taking phenytoin. A total of 340 (57.3%) were taking no AEDs. If a patient experienced seizures during titration, short-term treatment with a benzodiazepine was permitted. Seizures were individually recorded by date, time of occurrence, and type: simple partial (SPS), complex partial (CPS), generalized tonic (GTC), GTC and partial, and mixed partial. Incremental increases above target dose to toxicity were allowed if seizure control was inadequate. The blind was maintained by having patients simultaneously increase or decrease both capsules and tablets (one active, one placebo). If toxicity coexisted with inadequate seizure control, the patient exited the study. Completeness was monitored with pill counts at each visit.

Randomization was done for each site using varying block sizes. To randomize a patient, the nurse coordinator/site investigator telephoned the study's Data Coordinating Center (DCC) where a staff member assigned a nonconsecutive, site-specific patient number from a computer generated randomization list. This patient number corresponded to a patient drug kit in the site's pharmacy. A prescription for the specified drug kit was then prepared for the patient, who usually took the first dose of study drug at enrollment 239 patients (40.3%) were taking enzyme-inducing medications were allowed save chronic AEDs. Additional exclusions that would significantly affect the response to treatment. All comedication use excepting those conditions likely to lead to a life expectancy of less than 12 months, progressive neurologic disease, or conditions that would significantly affect the response to treatment. All comedications were allowed save chronic AEDs. Additional exclusion criteria included those with severe psychiatric conditions, current alcoholism, illicit drug use, or a history of noncompliance.

Number Randomized N = 593

Number on Carbamazepine n = 198

Number on Gabapentin n = 195

Number on Lamotrigine n = 200

Number Lost to Follow-Up (Primary Reason) = 56

Withdrew = 28

Lost = 4

Death = 14

Other = 10

Number Discontinued (Primary Reason) = 71

Adverse Events = 54

Uncontrolled Seizures = 3

Number Included in Primary Analyses = 197

Number Excluded = 1

(site terminated)

Number Lost to Follow-Up (Primary Reason) = 48

Withdrew = 23

Lost = 7

Death = 9

Other = 9

Number Discontinued (Primary Reason) = 51

Adverse Events = 34

Uncontrolled Seizures = 6

Number Included in Primary Analyses = 194

Number Excluded = 1

(site terminated)

Figure 1. Flow diagram of patients’ progress through the study.

Results. Patient demographics. Of 1,358 patients screened for possible enrollment, 593 met inclusion criteria (figure 1). Enrollment continued from January 1998 to April 2002. All patients were eligible to remain in the trial for 12 months with the option of continuing an additional 12 months. Final follow-up visits occurred in April 2003. Patients were randomly and equally assigned to one of three treatment groups: GBP (n = 195), LTG (n = 200), and CBZ (n = 198).

The main reasons for exclusion (not mutually exclusive) were under minimum age (n = 97), no seizure during preceding 3 months (n = 187), satisfied with current treatment (n = 147), unstable medical condition (n = 162), questionable compliance (n = 131), unwilling to enter study (n = 131), and unable to give consent (n = 143).

The most common seizure type was CPS (251/581; 43.2%), followed by GTC, SPS, GTC and partial, and mixed partial (see table E-1 on the Neurology Web site at www.neurology.org). There were no significant differences across treatment groups. Similarly, primary etiology did not differ significantly across groups, the most common of which was cerebral infarction (177/592; 29.9%), followed by arteriosclerosis (93/592; 15.7%) and head trauma (42/592; 7.1%, see table E-1). Unknown causes accounted for 24.0% (142/592) with all other causes at less than 2% each.

The majority of patients had vascular disease as evidenced by concurrent medical problems such as hypertension (391/593; 65.9%), stroke (302/593; 50.9%), and cardiac disease (298/592; 50.3%), which was cerebral infarction (177/592; 29.9%), followed by arteriosclerosis (93/592; 15.7%) and head trauma (42/592; 7.1%, see table E-1). Unknown causes accounted for 24.0% (142/592) with all other causes at less than 2% each.

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disease (286/593; 48.2%). At baseline, mild cognitive impairment was found in 35.0% (207/592), and neurologic findings included gait disturbances (312/593; 52.6%), abnormal sensory examination (183/593; 30.9%), memory problems (153/593; 25.8%), abnormal station (140/593; 23.6%), diminished motor power (132/593; 22.3%), and abnormal coordination (86/593; 14.5%).

**Study drug doses and serum levels.** Total daily doses of the study drugs approached target doses. At 6 weeks mean dosages were GBP 1,424 ± 285 mg/day, CBZ 558 ± 144 mg/day, and LTG 131 ± 34 mg/day. At 52 weeks, mean dosages were GBP 1,422 ± 288 mg/day, CBZ 582 ± 218 mg/day, and LTG 152 ± 33 mg/day.

Mean serum levels at 6 weeks were GBP 8.67 ± 4.83 µg/mL, CBZ 6.79 ± 2.92 µg/mL (unbound 1.0 ± 0.45), and LTG 2.87 ± 1.60 µg/mL. At 52 weeks, mean serum levels were GBP 8.54 ± 5.57 µg/mL, CBZ 6.48 ± 3.72 µg/mL (unbound 0.81 ± 0.43), and LTG 3.46 ± 1.68 µg/mL.

Dosage reductions for side effects occurred in 31.3% (171/547) while dosage increases above target for inadequate seizure control occurred in 21.4% (117/547). Dosage increases above target occurred more often in patients receiving LTG as compared to CBZ (27.1% [51/188] vs 14.0% [25/179], p = 0.002). Overall, medication compliance was 89% without significant group differences.

**Outcome measures.** Of 590 patients enrolled and not administratively terminated 276 (46.8%) completed 1 year in trial. The overall three-group comparison was significant (p = 0.00022). In paired-group comparisons, CBZ had more early terminators than either GBP (p = 0.008) or LTG (p < 0.0001). Reasons for early termination are listed in table E-2. Fewer LTG patients terminated for adverse reactions than either CBZ (p < 0.0001) or GBP (p = 0.015) patients. Relatively few patients exited the study due primarily or in part to uncontrolled seizures, with no differences among treatment groups. Times to early termination before 12 months and before 2 months are shown in the Kaplan-Meier curves (figures 2 and 3).

Between weeks 4 and 5 (see figure 3) the groups began to separate with better retention for LTG. When early terminations for adverse events occurring during the 6-week titration phase were considered, there were fewer LTG patients terminating for adverse events (8/199; 4.0%) than for either CBZ (41/199; 20.8%; p < 0.0001) or GBP (29/194; 14.9%; p = 0.0002).

Early terminators had a mean age of 73.0 (SE = 0.42) while completers had a mean age of 71.5 (SE = 0.45) (p = 0.0193). With respect to serum levels of early terminators, the last available values before termination were LTG (n = 60) mean = 2.67 µg/mL, SD 2.29 µg/mL, 95% CI 2.08 to 3.26 µg/mL; GBP (n = 69) mean = 10.14 µg/mL, SD 9.45 µg/mL, 95% CI 7.87 to 12.41 µg/mL; CBZ (n = 85) mean = 4.95 µg/mL, SD 3.44 µg/mL, 95% CI 4.21 to 5.69 µg/mL; free CBZ (n = 85) mean = 0.69 µg/mL, SD 0.52 µg/mL, 95% CI 0.58 to 0.80 µg/mL.

**Efficacy.** Seizure freedom, a secondary outcome measure, was analyzed at 3, 6, and 12 months after start of treatment. Patients remaining in the study dropped to 402 at 3 months (LTG 157, GBP135, CBZ 110), to 333 at 6 months (LTG 132, GBP 113, CBZ 88), and 276 at 12 months (LTG 111, GBP 95, CBZ 70). Of those remaining in the study for 3, 6, and 12 months, the seizure-free rates were 63.2% at 3 months (LTG 63.1%, GBP 62.6%, CBZ 64.5%), 58.6% at 6 months (LTG 56.6%, GBP 56.6%, CBZ 64.8%), and 53.3% at 12 months (LTG 51.4%, GBP 47.4%, CBZ 64.3%). There were no noteworthy group differences (overall p values: 0.93 at 3 months, 0.39 at 6 months, and 0.09 at 12 months). When seizures occurring during the 6-week titration phase were excluded, seizure-free rates increased to 80.1% at 3 months (LTG 80.3%, GBP 80.0%, CBZ 80.0%), to 70.6% at 6 months (LTG 68.2%, GBP 71.7%, CBZ 72.7%), and to 63.4% at 12 months (LTG 61.3%, GBP 60.0%, CBZ 71.4%). Again, there were no significant differences (overall p values: 1.00 at 3 months, 0.73 at 6 months, and 0.27 at 12 months).

We considered time to first, second, fifth, and tenth seizure during the first year. A total of 233 patients had at least one, 182 at least two, 101 at least five, and 54 at least 10 seizures. The log rank statistics for overall group comparisons were not different for any of these time to seizure(s) analyses (p = 0.18, 0.13, 0.74 and 0.95). Figure 4 shows the graphic for time to first seizure. When seizures during the 6-week titration period were excluded, these analyses were still not different (p = 0.39, 0.19, 0.11, and 0.34). Here, however, LTG patients tended to do worse for time to first and second seizure, and GBP patients tended to do better for time to fifth seizure than the other groups. Again, the results were not significant.

A third measure of efficacy that was considered was seizure-free retention. These analyses included all patients
at all rating periods and counted early terminators as if they had had seizures. As with the seizure-free rate analyses, this variable was analyzed at 3, 6, and 12 months, and was done using 1) all seizures and 2) excluding seizures occurring during the 6-week titration period. For all seizures the seizure-free retention rates were 43.1% at 3 months (LTG 49.7%, GBP 43.3%, CBZ 36.0%), 33.1% at 6 months (LTG 37.2%, GBP 33.0%, CBZ 28.9%), and 24.9% at 12 months (LTG 28.6%, GBP 23.2%, CBZ 22.8%). A significant difference was seen only at 3 months (overall \( p < 0.001 \)) as compared with the CBZ group \( (p = 0.006) \). When seizures occurring during the 6-week titration period are excluded, LTG patients \( (63.3\%) \) again did better at 3 months \( (p = 0.001) \) than CBZ patients \( (44.7\%) \) with GBP patients in between \( (55.7\%) \). Similarly, at 6 months LTG patients \( (45.2\%) \) also had better seizure-free retention \( (p = 0.009) \) than did CBZ patients \( (32.5\%) \). The differences at 12 months were not significant \( (overall\ \text{overall\ } p = 0.16) \).

**Adverse reactions.** Table E-3 reports the systemic and neurotoxicities that occurred during the first 12 months for those patients having at least one submitted follow-up form. Significantly more patients on GBP had weight gain during the first 12 months than either those on CBZ \( (p = 0.002) \) or LTG \( (p = 0.001) \). More patients on GBP had large weight gain \( (>18 \text{ pounds}) \) than those on CBZ \( (p = 0.005) \) or LTG \( (p = 0.014) \). Water retention was significantly greater with GBP than with CBZ \( (p = 0.004) \) or LTG \( (p = 0.02) \). More patients lost weight with LTG than with GBP \( (p = 0.002) \), but the proportion of patients who gained \( (47.5\%) \) or lost weight \( (36.1\%) \) on LTG was similar. Hypersensitivity (rash of any degree) occurred more frequently with CBZ than with LTG \( (p = 0.007) \). Of seven patients hospitalized for hypersensitivity reaction, six were in the CBZ group and one was treated with LTG. Hyponatremia (sodium less than 130 mg %) occurred more frequently in CBZ than in GBP patients. There were no significant differences in other systemic toxicities. Considering neurotoxicities, there were no differences among the treatment groups over 12 months. Severe neurotoxicities were reported in 43 patients \( (8.1\%) \).

Thirty-nine deaths occurred during the trial: 15 in the CBZ group, 11 GBP, and 8 LTG. There was no clustering of causes for death in any of the treatment arms to suggest a link between drug and cause of death. None of the deaths was determined to be clearly due to study drug. One patient died 2 weeks after stopping study drug due to a probable hypersensitivity reaction that led to multiple system organ failure. This patient was in the CBZ arm and had received phenytoin for 1 week before enrollment, thus obscuring the proximate cause. Other causes of death ranged from cardiac and pulmonary disease to sepsis and cancer.

**Discussion.** This multicenter clinical trial of seizures in an older population is the largest to date. When the protocol was designed, two newly approved AEDs (GBP and LTG) appeared to offer advantages over the standard AEDs, particularly with respect to their pharmacokinetic and side effect profiles. There was a need to compare the new drugs with a standard AED. Phenytoin, valproic acid, and CBZ were considered, and CBZ was selected due to its worldwide acceptance as a treatment of choice for partial onset epilepsy.

Hepatic and renal function decline with age; thus, lower total daily doses are usually suggested for older adults. Hence, selection of appropriate target doses and titration schedules were major issues and discussed in depth with our outside advisory committee. We also consulted the then limited available literature and the relevant pharmaceutical companies. The selected target doses were generally lower than what might be considered standard doses for younger adults, recognizing that the protocol contained built-in mechanisms for both decreasing and increasing the doses at any time as clinically indicated. Further, the titration schedules were slower than usually employed in clinical practice. We found that final dosages of the study drugs were similar to the target doses, and the range of serum levels for the three drugs remained low to moderate and relatively stable throughout the trial.

The patients were newly diagnosed with epilepsy and treated with AED monotherapy, circumventing complications associated with add-on and cross-over trials. Concurrent medical diseases were allowed to ensure that the study would reflect medical realities of the elderly population. Because of the high recurrence rate in the aged after a first seizure \( (66\% \text{ to } 90\%) \), the potential consequences of recurrent seizures, and the high incidence of risk factors such as cerebrovascular disease, we felt the occurrence of at least one seizure during the 3-month window preceding enrollment was a justified enrollment criterion. Complex partial seizures alone were the most common seizure type \( (43.2\%) \). Only 25.3% presented with GTCs alone, a lower proportion than reported in epidemiologic studies that predominantly include younger adults. These findings are likely due to a different predominate etiology for seizures in older patients—namely, vascular disease involving the anterior and middle cerebral arteries. One would therefore expect an increased occurrence of seizures that originate in the frontoparietal region.

The high incidence of seizures in older patients

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**Figure 4.** Percentage of patients remaining seizure-free over time (time to first seizure).
has not been widely appreciated. We suspect that CPS may not be recognized due to their subtle or different clinical presentations. For example, CPS may present only with periods of confusion or staring for brief periods with little if any motor activity (automatisms). Of the 25.3% with GTCs alone, none had evidence of primary generalized epilepsy, for example generalized spike-wave discharges in the EEG.

Our primary outcome measure, retention in trial for 12 months, showed a highly significant difference with CBZ showing poorer retention than either GBP or LTG. The data suggest that this is not due to differences in efficacy. Methods used to evaluate efficacy included 1) percent of patients seizure-free for 12 months, 2) time to first seizure, and 3) seizure-free retention rate. There were no significant differences using methods 1, 2, or 3. Of the patients remaining in the study for 52 weeks, the seizure free rate was highest with CBZ. Methods 1 and 2, however, favor a poorly tolerated drug, inasmuch as seizures could only be counted in patients who remained in the study, and patients who withdrew might also be the ones likely to have recurrent seizures. A higher seizure-free retention rate was found with LTG using an intent-to-treat analysis (method 3), a method favoring a well-tolerated drug. In fact, at 3 months, there was a significantly better seizure free rate for LTG. This difference disappeared at 6 and 12 months. (See Outcome measures, efficacy.) Differences in efficacy were less evident when seizures occurring during the 6-week titration phase were ignored. The primary factor accounting for patients remaining in the trial, therefore, appears to be the incidence of adverse events and not poor seizure control.

Although the mean age of early terminators was greater than that of completers (73 vs 71.5, \( p = 0.0193 \)), we do not believe this difference materially affected the results of the trial. With respect to serum levels at or close to the time of termination, we found that the levels of LTG and CBZ were slightly less than those seen during the maintenance phase of the study (after 6 weeks). On the other hand, GBP at termination was above those levels obtained during the course of the trial. The lower termination levels of CBZ (mean 4.95 \( \mu g/mL \)) and free CBZ (mean 0.69 \( \mu g/mL \)) than those found during maintenance add support to the thesis that the choice of initial dose and titration schedule for this drug was conservative and thus not a sufficient reason for its intolerability. The opposite may be true for GBP where higher termination doses were found than those obtained during maintenance.

Because our study population was made up predominantly of men, it is possible that these results may not be generalizable to the population at large. It is noted, however, that seizure occurrence in younger women is influenced by hormonal fluctuations—not a factor in older patients. Thus, we postulate that the results of this study should be broadly applicable.

The protocol allowed for increasing the dose beyond target if seizures were not controlled and decreasing the dose to reduce/eliminate side effects. During the first 12 months, dosage reductions varied from 30.7% for CBZ to 32.2% for GBP. During the titration phase, dosage reduction ranged from 11.7% for LTG to 16.2% for CBZ. Had the initial dose for any of the treatments been too high, a greater drop-out rate would have been expected for that drug during the first 2 weeks, recalling that the dose of CBZ was not changed during that time, and that its titration schedule was slower than usually employed in clinical practice. In fact, retention was similar in the three treatment arms up to the end of the third week (see figure 3), with differences becoming evident during weeks 4 to 6. Thus, the dosing schedules did not significantly alter the outcome of the study.

Would use of an extended release preparation of CBZ (ER-CBZ) have altered the results? Because of the longer CBZ half-life in the elderly, due largely to reduced hepatic metabolism, the peak-trough effect is potentially less prominent. This would mitigate a possible advantage of an ER-CBZ. Moreover, the relatively lower CBZ serum levels in this population compared to those usually sought in younger adults would also reduce the impact of an ER-CBZ. We therefore believe that using an ER-CBZ would not have led to a significant difference in our results.

Appendix

Chairmen’s Office: R. Eugene Ramsay, MD, Miami, FL, Study Co-Chairman; A. James Rowan, MD, Bronx, NY, Study Co-Chairman; Flavia Pryor, RN, MPH, Miami, FL, National Study Coordinator. Cooperative Studies Program Coordinating Center (CSPCPC), Perry Point, MD; Joseph F. Collina, CNM, Director; Susan Stinnett, Linda Linzy, Colleen Girgler, Chuanshue Lee, Pat Grubb, Beverly Calvert. Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCPCCC), Albuquerque, NM: Mike Sather, PhD, FASHP, Cindy Colling, RN, MS, Kathy D. Boardman, RN, Jenine Peterson, BS, Data Safety Monitoring Board. John Pellock, MD, Dan Berlowitz, MD, Carla Herman, MD, Steven Schachter, MD, James Willmore, MD, Nancy Temkin, PhD, Perry Lee, PhD. Human Rights Committee, Cooperative Studies Program Coordinating Center, Perry Point, MD: Clint McSherry, PhD, Rev. James Jones, James Crothers, Anthony Harris, MD, Lettie Carr, Rose Kurz, Thaddeus Prout, MD, Adele M. Gilpin, PhD, JD, Alan Fix, MD, MS, Mary Zorzi. Participating centers (VA Cooperative Study #428 Group): Birmingham, AL—R. Edward Faught, MD, Dinauer Wilhe, Cheryl Hall, Boston, MA—Thomas Browne, MD, Barbara Dworetzky, MD, Menisha Thakore, MD, Sheila Savickis, RN, Bronx, NY—Maria Muxfledt, MD, Martin Gluck, MD, PhD, Helene Price, MD, Linda Tuchman, LPN, Chicago, IL—Mary Lou Tonyanovich, MD, Cristina Orfei, MD, Rita Shapire, DO, Susan Winkler, PharmD; Dallas, TX—Gregory Carter, MD, PhD, Amy Choute, BS; Denver, CO—Mark Spitz, MD, Jacqui Bainbridge, PharmD; Gainesville, FL—Bassim Uthman, MD, Brenda Smith, RN; Hines, IL—Meenal Mandani, MD, Sudha Gupta, MD, Katarzyna Wisniewski, MI, FL—John DeTooles, MD, Juanita Johnson, BS, New Orleans, LA—Tim Frederick, MD, Kathryn Lalrusse, RN, Oklahoma City—Peggy Wisdom, MD, K.J. Oommen, MD, Terry Rogers-Neame, MD, Richard Dasheiff, MD, Neil Holland, MD, Kersi Bharucha, MD, Marsha DeWitt, RN, Phoenix, AZ—Richard Matthews, MD, Jaewant Sachdev, MD, Halina Roznowski; Pittsburgh, PA—Anne Van Cott, MD, Regina Fenton, MSN; Portland, OR—Martin D. Salsinsky, MD, Debbie Johnstone, RN; Richmond, VA—Alan Towne, MD, Heather Shebelski, RN; San Diego, CA—Vincent Iragui, MD, Karen Wetzal, PA; San Francisco, CA—William Marks, MD, Elaine Lanier, RN; San Antonio, TX—Jose Cavaos, MD, Laura Moreno, RN.

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